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Gestational diabetes mellitus – news '2009

Cukrzyca ciążowa – aktualności '2009

PATHOGENESIS AND DEFINITION

Pregnancy is characterized by disturbances in metabolic balance between the action of hyperglycemizing and hypoglycemizing hormones, which results in a state of physiological insulin resistance. Despite gradually increasing production of insulin, there is an increase in the secretion of hyperglycemizing hormones produced by the placenta. First, these are progesterone, estrogens and cortisol, then placental lactogen (hPL), growth hormone (GH) and finally prolactin. Diabetogenic action of the above mentioned hormones causes a decrease in glucose tolerance in the mechanism of increasing insulin resistance, which results in a decrease of glycogen stored in the liver, an increase in hepatic gluconeogenesis and its decreased peripheral utilization, particularly in skeletal muscles. In a healthy pregnant woman insulin resistance is overcome by compensatory secretion of insulin, which ensures normoglycemia [19]. However, in predisposed women (Table 1) [25] increasing insulin resistance is accompanied by a defect in secretion and production of insulin, which eventually leads to the development of various disturbances in glucose tolerance which in pregnancy bear the common name of gestational diabetes mellitus (GDM) [8, 20]. According to the WHO definition, GDM means every disturbance in carbohydrate tolerance, regardless of its severity, which occurred for the first time in current pregnancy or it was diagnosed at that time [16]. It should be assumed that it is most frequently type 2 diabetes, having its onset in pregnancy or existing but not detected before pregnancy. It is supported by the fact that as much as 30–50% of

Table 1. Risk factors for developing gestational diabetes mellitus

Positive family history of diabetes
Woman's obesity before pregnancy
Excessive gain of body weight during pregnancy
Age > 25 years
GDM in history
IGT in history
Delivering a child with the mass > 4000g
Delivering a child with congenital defects, macrosomia in history, unexplained intrauterine and perinatal deaths
Hydramnion
Glycosuria during current pregnancy

women who were diagnosed with gestational diabetes mellitus during pregnancy develop manifest symptoms of type 2 diabetes within 10 years of delivery [9]. In the last few years many new reports have appeared concerning pathogenesis of insulin resistance in GDM, not related to the hormonal basis, since it is a primary disturbance and dominant over the impaired function of β islet cells of the pancreas. The reports showed a relationship between the presence of central accumulation of adipose tissue and an increase in peripheral tissue resistance to insulin. The abdominal adipose tissue, as a metabolically active organ of internal secretion, produces many biologically active adipocytokines which may play a role in pathogenesis of insulin resistance. Tumour necrosis factor alpha (TNFα) and leptin have been reported to be implicated in insulin resistance of pregnancy [14]. Kirwan et al. [11] found that the changes in concentration of TNFα were the most significant predictor of insulin resistance using multivariate analysis. A potential concern with that study is that insulin sensitivity in the group with gestational diabetes was half of that in the obese pregnant controls, but the levels of TNFα were equivalent. In addition to TNFα and leptin, recently identified hormones emanating from fat are adiponectin and resistin. Adiponectin enhances insulin sensitivity and resistin increases insulin resistance.

Reports in literature concerning adiponectin concentrations in pregnancy complicated with GDM are contradictory. Certain authors indicate a decrease in its concentration together with an increase in insulin resistance in pregnancy, which may confirm that it is a cytokine participating in the pathogenesis of insulin resistance [17]. However, the research of many other authors, such as Thyfault et al., shows that adiponectin concentration may be related to the degree of insulin resistance and severity of disturbances in carbohydrate metabolism. They demonstrated a statistically significant decrease in adiponectin only in patients with class B GDM (pregestational diabetes) and A2 GDM (diabetes treated with insulin and diet); pregnant women controlled with a diabetic diet only did not present a significant decrease in this cytokine, which is also confirmed by Polish studies [13, 21]. Moreover, these authors suggest that there are ethnic differences which condition adiponectinemia in pregnant women [21]. Estimation of resistin in mice seemed to be promising, but it was not clearly confirmed in people. mRNA expression of resistin in the placenta was established, with more resistin-gene expression in the term placenta than in first-trimester chorionic tissue and four-fold higher levels in the plasma during pregnancy. Expression of the resistin gene in adipose tissue in pregnancy did not change significantly during gestation, which requires a further study [24]. At the moment, the hormonal basis looks a more likely candidate in the induction of insulin resistance in pregnancy.

INCIDENCE

It is estimated that GDM is the most common metabolic complication of pregnancy and the prevalence of diabetes during pregnancy varies significantly, reflecting general tendencies in the spread of type 2 diabetes in a given population in the world [10]. In the USA this pathology affects from 1.4 to 12.3% of all pregnant women depending on the state of the country [5]. In the UK, GDM is an increasingly common condition, affecting 7% of all pregnancies [6]. In Poland there are few studies concerning the subject and according to Wójcikowski, the prevalence of GDM in different parts of Poland ranges from 2.0% to 3.8%, 3.4% on average [21].

CLINICAL PICTURE

Due to the asymptomatic course of GDM, screening examinations should be performed which will allow quick detection of the disease and can prevent adverse consequences for the mother, the fetus and the newborn. The tissues of the developing fetus are very sensitive to metabolic disturbances occurring in the mother's organism, especially to the concentration of glucose which

passes through the placenta in the way of facilitated diffusion. Hyperglycemia in the mother and subsequently also in the fetus causes an increase in the secretion of fetal insulin and increased concentration of growth factors, which in consequence leads to an increase in / growth of insulin sensitive tissues, particularly adipose tissue, muscles and internal organs. This mechanism results in macrosomia which is recognized when the birth mass of a child exceeds 4000 grams or when it is large for gestational age (LGA). It is the most frequent complication concerning the fetus as it affects from 10% to 45% of GDM patients [12]. Hyperglycemia and hyperinsulinemia not only increase a risk of macrosomia but they are also responsible for many complications in the fetal and neonatal life (Table 2) [15]. Since GDM develops mainly in II and III trimesters of pregnancy, it most frequently disturbs growing and maturing processes in the fetus and to a lesser extent it induces abnormalities in organogenesis. It should be emphasized that all disturbances in the intrauterine development affect psychomotor development of a child and later an adult and they increase the incidence of key elements of the metabolic syndrome. Undiagnosed, thus untreated or badly treated GDM also creates a risk of a number of complications in a pregnant woman (Table 3) [15]. There is a constant relationship between an increase in blood glucose concentration in a pregnant woman and a risk of complications in the mother and fetus, therefore it has been decided that the mean circadian value of glycemia should not definitely exceed 95mg% (Table 4) [15, 25].

Table 2. Influence of diabetes on the development of the fetus and the condition of the neonate

Risk for the child
Spontaneous abortions
Intrauterine death of the fetus
Perinatal mortality
Developmental defects
Intrauterine growth disturbances (IUGR, macrosomia)
Postpartum complications (hypoglycemia, perinatal injuries, respiratory disturbances syndrome, polycythemia, jaundice, hypocalcemia and hypomagnesemia, circulatory insufficiency)

Table 3. Influence of diabetes on the course of pregnancy

Risk for the mother
Abortion, premature labour
Increased risk of hypertension and preeclampsia
Development of type 2 diabetes in the future
Increased risk of urinary tract infections
Increased percentage of Caesarean sections
Premature labour, hydramnion

Table 4. GDM compensation criteria

Fasting glycemia	60–90 mg/dl (3.3-5.0 mmol/l)
Preprandial glycemia	< 100 mg/d (5.5 mmol/l)l
Postprandial glycemia (1-2 h after a meal)	< 120 mg/dl (6.7 mmol/l)
Mean circadian glycemia	95 mg/ dl (3.3 mmol/l)
HbA1C	<6.1%
Fructosamine concentration	220–285 μmol/l
Absence of hypoglycemia	
Aglycosuria	

DIAGNOSTIC ALGORITHM

Risk factors for GDM occur in approximately 40–60% of pregnant women, so recommendations of the Polish Gynecological Society and the Polish Diabetological Society concerning examination of women towards diabetes seem to be well justified [25]. The recommended algorithm for detection of this pathology begins with an initial assessment of glucose concentration when a woman is found to be pregnant, and further management has two stages including a screening test and a diagnostic test (Fig. 1) [25]. The screening test (glucose challenge test, GCT, O'Sullivan test) consists in the oral administration of 50-gram glucose load to every pregnant woman between the 24th and 28th weeks of gestation in ambulatory care setting at any time of the day, and the test does not need to be performed on an empty stomach. Glucose is measured once only, 60 minutes after administration. When the result of the GCT is normal, a diagnostic test with 75 grams of glucose should be performed (oral glucose tolerance test, OGTT), which requires fulfilling slightly different laboratory conditions. It should be performed after at least 3 days of a normocarbohydrate diet, always on an empty stomach (minimum 8 hours after the last meal), estimating fasting glycemia and after 120 minutes from the ingestion of a glucose solution (75g dissolved in 250–300 ml of water, within 3–5 minutes). During the examination the patient should be sitting, without making any effort and without smoking. With a normal result of a screening test and a abnormal diagnostic test, a diagnostic test should be repeated in the 32nd week of gestation.

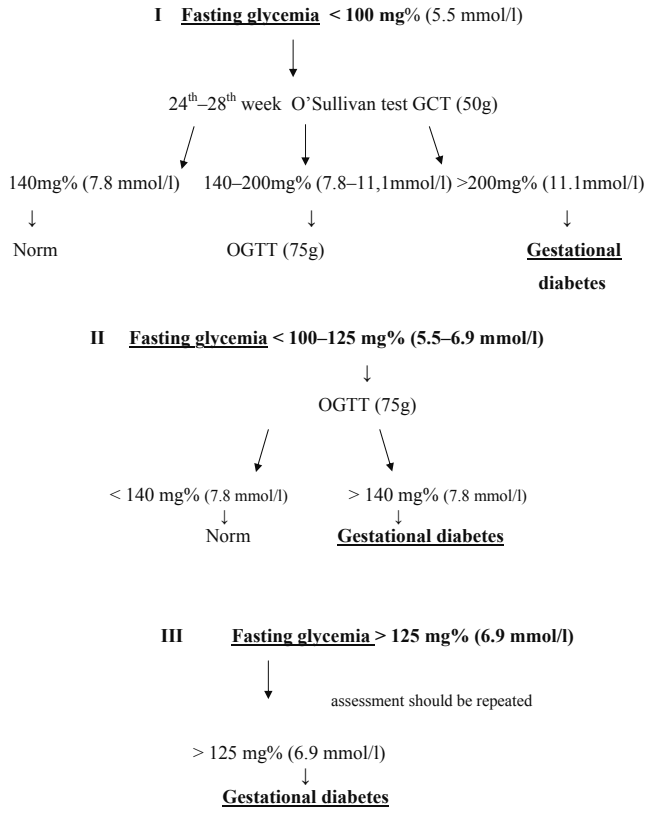

Fig. 1. Diagnostic algorithm of gestational diabetes mellitus

In a group of women with risk factors for GDM (Table 1) only a diagnostic test can be recommended and it should be performed at the time when a woman is found to be pregnant, and possibly repeated at the usual screening time, between the 24th – 28th weeks. In this case GDM cannot be diagnosed on the basis of a screening test only [3].

It is recommended that assessment of glucose concentration should be performed in venous blood plasma, both during the examination on an empty stomach and at the time of a diagnostic test; however, in a screening test estimation in capillary blood is acceptable. Values of glycaemia assessed in capillary blood are approximately 10% lower than fasting plasma levels, but they are identical after a meal. Diagnostics of hyperglycemic conditions should not be performed during an acute disease, injury, operation or during short-time intravenous use of drugs increasing blood glucose concentration (steroids, β-mimetics).

THERAPEUTIC MANAGEMENT

The basis for achieving full metabolic compensation is following an appropriate diabetic diet which should ensure normoglycemia and aglycosuria, prevent ketosis and at the same time cause a proper increase in body mass, adequate to gestational age (Table 4) [25]. An integral part of GDM treatment should be physical activity which has an influence on pathogenesis of carbohydrate metabolism disturbances as it increases insulin sensitivity of tissues, thus markedly decreasing insulin resistance and improving tolerance of glucose. If normoglycemia is not achieved after the introduction of a diabetic diet and following it for 7 consecutive days, insulin therapy based on human insulins should be implemented. The only appropriate model of treatment is intensive insulin therapy, although insulin doses administered with meals are often introduced gradually, depending upon postprandial glycemia. Since insulin resistance in pregnancy is the greatest in the morning hours, which is associated with an increased concentration of hyperglycemizing hormones produced by the placenta, hyperglycemia is most frequently observed on an empty stomach and after breakfast. At present, long-term analogues are not recommended, short-term analogues, however, are not contraindicated [18,25]. Immediately after delivery a demand for insulin markedly decreases and in most patients insulin therapy as well as a diabetic diet should be withdrawn. In GDM therapy, administration of oral blood glucose-lowering drugs is not allowed [7].

CURRENT STATE

GDM is the most common metabolic disorder complicating the course of pregnancy, which is usually resolved with its termination, although it remains a risk factor for type 2 diabetes for the mother. According to Kim et al. the incidence of this pathology ranges from 2.6 to 70% of pregnant women having a history of GDM, depending on the observation period from 6 weeks to 28 years. The risk increases significantly in the first 5 years after childbirth and it reaches its plateau 10 years after delivery [9]. Other retrospective studies conducted in this group of women found various disturbances in carbohydrate metabolism after delivery, depending on the population studied, within the range of 34.4% and 54%, respectively [4, 22]. Facing such a high risk of diabetes in the group of patients with a history of GDM, it is now recommended that a rediagnostics of carbohydrate metabolism disturbances should be made between 6th and 12th weeks after delivery, together with further observation of carbohydrate balance in the future [1, 25]. It should also be added that in adult offspring of mothers with GDM the risk of developing type 2 diabetes or pre-diabetes is significantly higher than in women with genetic predisposition or type 1 diabetes [2].

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SUMMARY

GDM is the most common metabolic disorder complicating the course of pregnancy and the prevalence of diabetes during pregnancy varies significantly. Due to the asymptomatic course of GDM screening examinations should be performed because the untreated disease increases a risk of complications both in the fetus and the neonate as well as in the pregnant woman. Although usually resolved with termination, GDM remains a strong risk factor for type 2 diabetes for the mother in the future, therefore rediagnostics of carbohydrate metabolism disturbances is necessary after delivery. The article presents the current state of knowledge about gestational diabetes regarding its pathogenesis, diagnostics, treatment and prognosis.

STRESZCZENIE

Cukrzyca ciążowa jest najczęstszym powikłaniem metabolicznym komplikującym przebieg ciąży, a jej częstość występowania jest zróżnicowana. Z uwagi na bezobjawowy przebieg choroby powinny być wykonywane badania przesiewowe, ponieważ nieleczona zwiększa ryzyko powikłań zarówno u płodu i noworodka, jak również u matki. Pomimo tego, że najczęściej ustępuje wraz z rozwiązaniem ciąży, to pozostaje silnym czynnikiem zachorowania matki na cukrzycę w przyszłości, zatem niezbędna jest rediagnostyka po urodzeniu dziecka. Artykuł przedstawia stan wiedzy na temat cukrzycy ciążowej w zakresie patogenezy, diagnostyki, leczenia i rokowania.